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First-in-human phase I/Ib study of the oral Werner (WRN) helicase inhibitor HRO761 in patients with microsatellite instability-high or mismatch repair deficient advanced solid tumors: Interim safety and efficacy analysis from HRO761 single agent dose escalation

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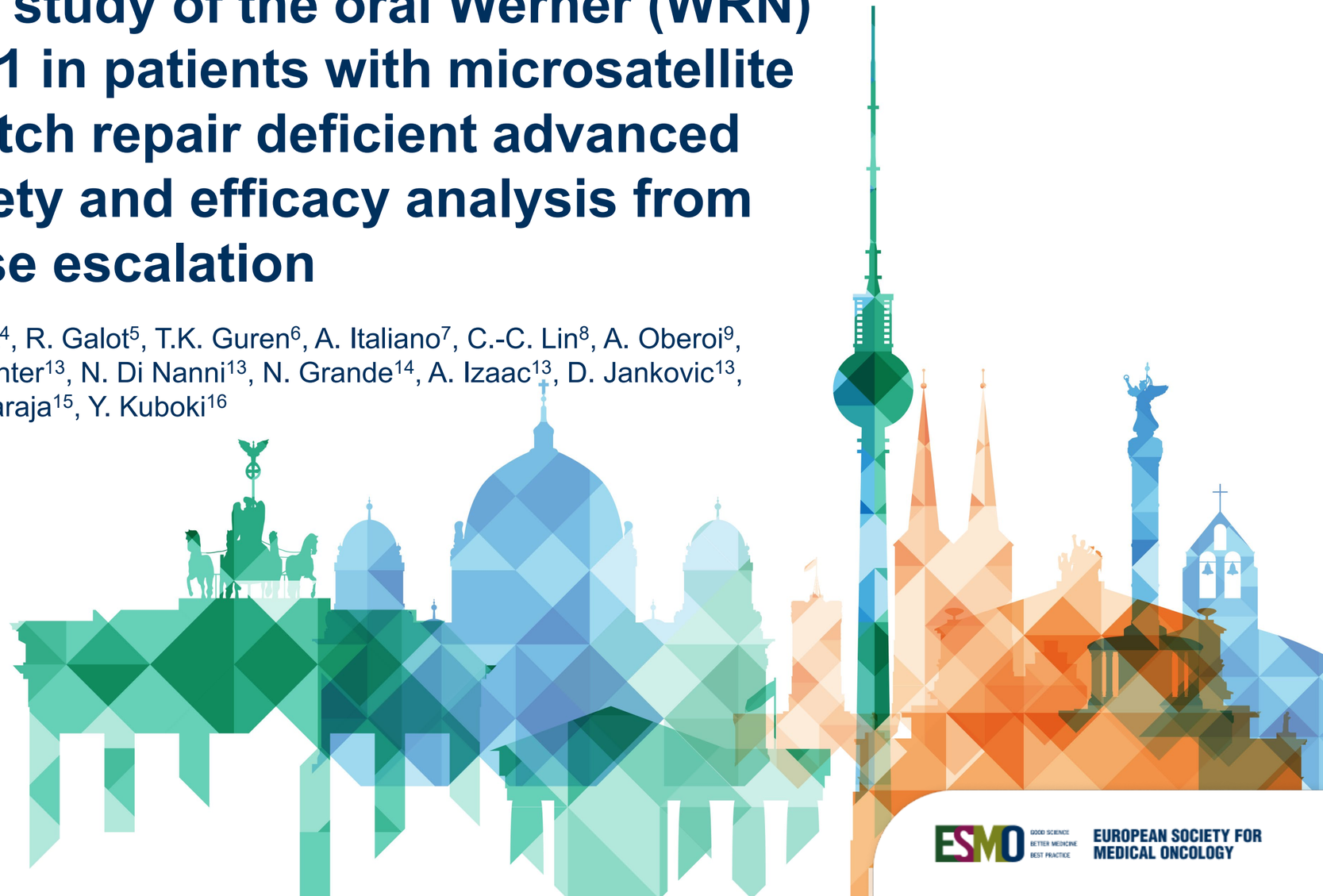

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Declaration of interests

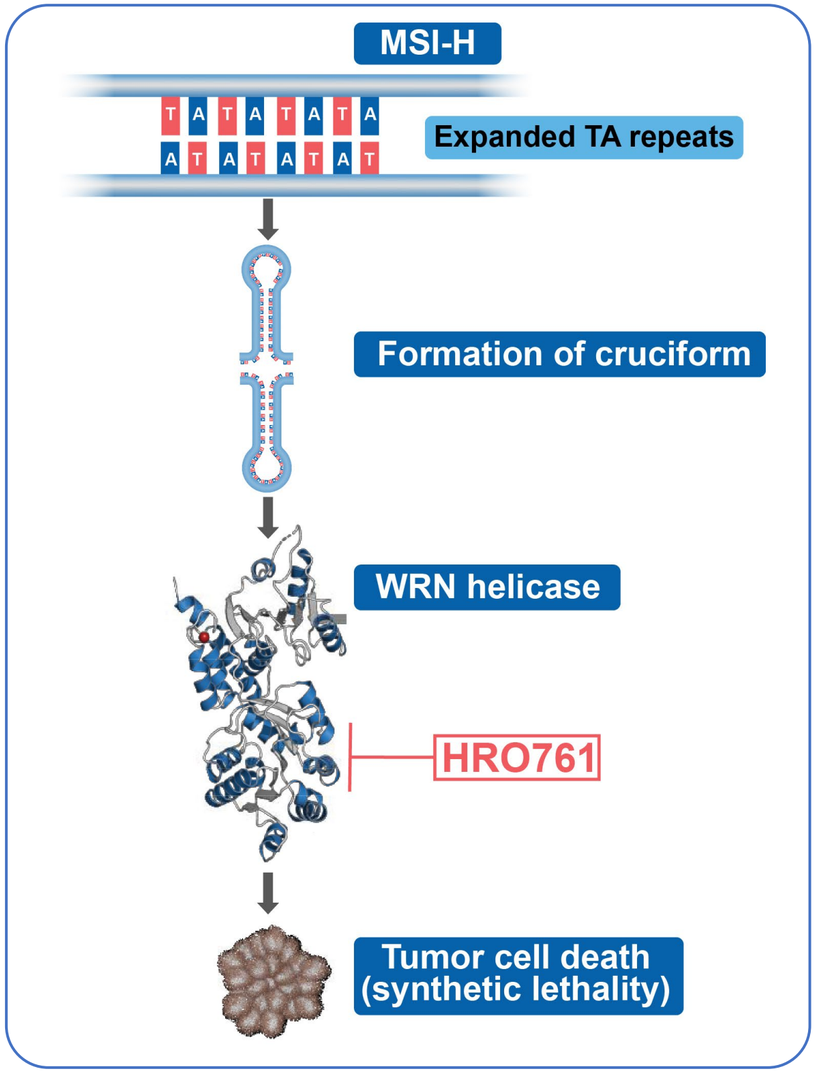
Michael B. Foote

Advisory board, personal: Bristol Meyers Squibb, Genzyme, Abbott Laboratories, Intera

Medical Education Talk, personal: Axiom Healthcare Strategies, Cancer Network, Horizon CME, OncLive

HRO761 is an oral WRN inhibitor for MSI-H cancers

- MSI-H cancers exhibit secondary structures of expanded TA-dinucleotide repeats that require unwinding by the WRN syndrome protein, a DNA helicase[1]
- WRN inhibition in MSI-H cells induces synthetic lethality through DNA damage, cell cycle arrest, and apoptosis[1,2]
- HRO761 is a potent, selective, allosteric WRN inhibitor that locks WRN in an inactive conformation[3]
- HRO761 induces strong, dose-dependent regression of tumors in MSI-H cell- and patient-derived xenograft models[3]



Adapted from Moschetta M, et al.[4]

MSI-H, microsatellite instability-high; WRN, Werner.

1. van Wietmarschen N, et al. *Nature.* 2020;586:292–298; 2. Chan EM, et al. *Nature.* 2019;568:551–556; 3. Ferretti S, et al. *Nature*. 2024;629:443–449. 4. Moschetta M, et al. *ESMO Congress*. 2023; Poster 719TiP.

Phase I dose finding of single agent HRO761 in patients with MSI-H/dMMR advanced solid tumors

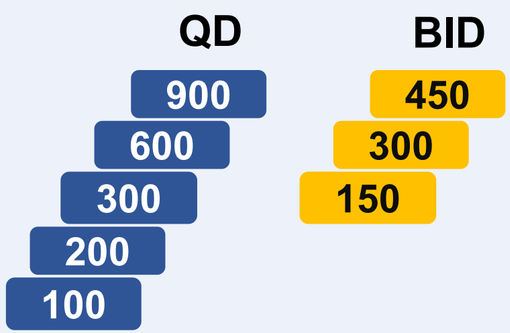
Data cutoff: June 15, 2025

Dose escalation N=57

Population

- MSI-H/dMMR solid tumors via IHC, PCR, or NGS
- Progression/intolerance to SOC
- CPI and chemo or TT required

Dose (mg)



Dose optimization N≈60

	Dose 1 (mg)	Dose 2 (mg)
CRC	n≈20	n≈20
Non-CRC	n≈10	n≈10

≤ 3 lines of systemic therapy

CRC: CPI, FP, and OX or IRI required

Non-CRC: CPI and chemo or TT required

Primary objectives

- Safety and tolerability
- Recommended dose and regimen

Secondary objectives

- PK profile
- Preliminary antitumor activity per RECIST v1.1

EU-CT number: 2022-502314-93; ClinicalTrials.gov ID: NCT05838768

BID, twice daily; chemo, chemotherapy; CPI, checkpoint inhibitor; CRC, colorectal cancer; dMMR, mismatch repair deficient; EU-CT, European Union-Clinical Trial; FP, fluoropyrimidine; ID, identifier; IHC, immunohistochemistry; IRI, irinotecan; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; OX, oxaliplatin; PCR, polymerase chain reaction; PK, pharmacokinetics; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care; TT, targeted therapy.

Baseline characteristics

Baseline characteristics	All patients (N=57)
Age (years), median (range)	56.0 (32–85)
Sex, n (%) Female / Male	 29 (50.9) / 28 (49.1)
Race, n (%) Asian / Black or African American / White / NR or UNK	 22 (38.6) / 2 (3.5) / 26 (45.6) / 7 (12.3)
ECOG PS, n (%) 0 / 1	 18 (31.6) / 39 (68.4)
Prior antineoplastic therapy, n (%) Number of regimens, n (%) 1 / 2	57 (100) 2 (3.5) / 9 (15.8)
≥ 3 Median (range)	46 (80.7) 4 (1–10)
Initial diagnosis, n (%)	
CRC*	33 (57.9)
Non-CRC Endometrial* Gastric/GEJ* Other	24 (42.1) 6 (10.5) 6 (10.5) 12 (21.1)

*Adenocarcinoma.

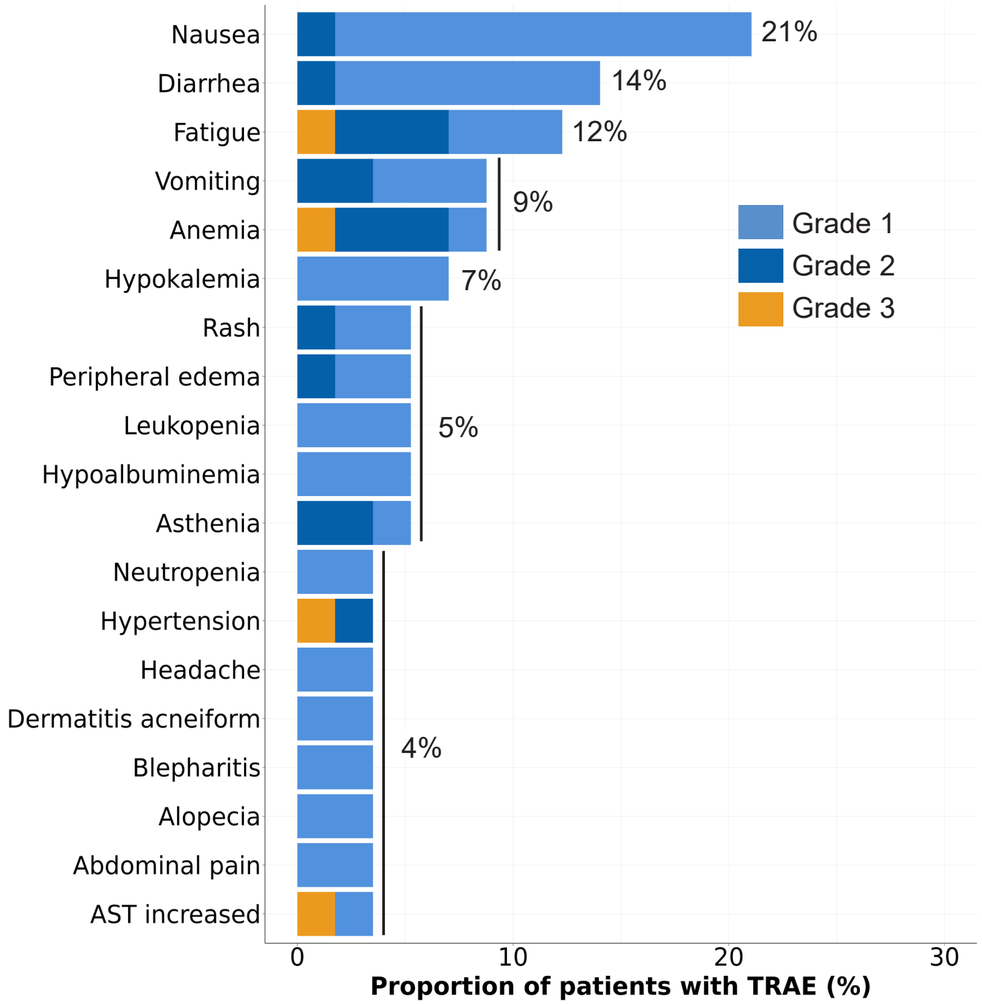
CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; NR, not reported; UNK, unknown.

HRO761 shows a favorable safety profile

Overview of all AEs by dose and regimen

	100 mg QD (N=8)	200 mg QD (N=10)	300 mg QD (N=4)	150 mg BID (N=6)	600 mg QD (N=10)	300 mg BID (N=5)	900 mg QD (N=9)	450 mg BID (N=5)	All (N=57)
AEs, n (%)	7 (87.5)	9 (90.0)	4 (100)	5 (83.3)	10 (100)	5 (100)	8 (88.9)	5 (100)	**53 (93.0)**
Treatment-related	**3 (37.5)**	**6 (60.0)**	**3 (75.0)**	**4 (66.7)**	**7 (70.0)**	**4 (80.0)**	**5 (55.6)**	**2 (40.0)**	**34 (59.6)**
AEs with grade ≥3, n (%)	4 (50.0)	6 (60.0)	2 (50.0)	3 (50.0)	3 (30.0)	4 (80.0)	4 (44.4)	0	**26 (45.6)**
Treatment-related	**1 (12.5)**	**2 (20.0)**	**0**	**0**	**0**	**2 (40.0)**	**3 (33.3)**	**0**	**8 (14.0)**
SAEs, n (%)	3 (37.5)	5 (50.0)	2 (50.0)	3 (50.0)	3 (30.0)	2 (40.0)	2 (22.2)	0	**20 (35.1)**
Treatment-related	**0**	**1 (10.0)**	**0**	**0**	**0**	**1 (20.0)**	**1 (11.1)**	**0**	**3 (5.3)**
AEs leading to dose interruption, n (%)	4 (50.0)	5 (50.0)	1 (25.0)	3 (50.0)	4 (40.0)	4 (80.0)	5 (55.6)	2 (40.0)	**28 (49.1)**
Treatment-related	**2 (25.0)**	**2 (20.0)**	**0**	**2 (33.3)**	**1 (10.0)**	**2 (40.0)**	**2 (22.2)**	**0**	**11 (19.3)**
AEs leading to dose adjustment, n (%)	0	0	0	0	1 (10.0)	0	2 (22.2)	0	**3 (5.3)**
Treatment-related	**0**	**0**	**0**	**0**	**1 (10.0)**	**0**	**1 (11.1)**	**0**	**2 (3.5)**
AEs leading to treatment discontinuation, n (%)	1 (12.5)	1 (10.0)	1 (25.0)	0	2 (20.0)	0	0	0	**5 (8.8)**
Treatment-related	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
DLT	0	0	0	0	0	0	1 (11.1)	0	**1 (1.8)**

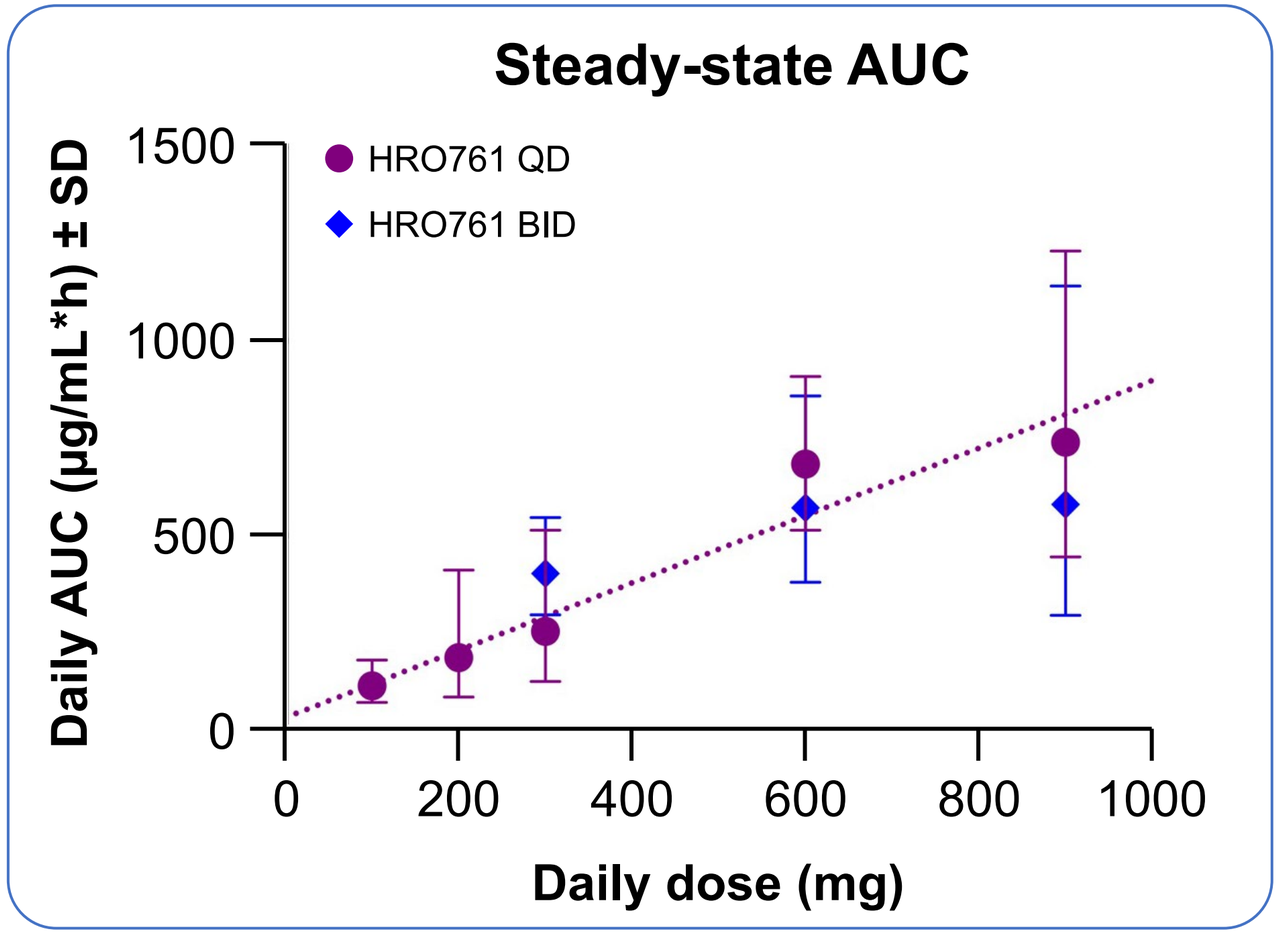
TRAEs occurring in 2 or more patients (N=57)



- Most common TRAEs were low-grade nausea, diarrhea, and fatigue
- One DLT of decreased EF without recurrence after dose reduction from 900 to 600 mg QD

AE, adverse event; AST, aspartate aminotransferase; BID, twice daily; DLT, dose-limiting toxicity; EF, ejection fraction; QD, once daily; SAE, serious adverse event; TRAE, treatment-related adverse event.

HRO761 shows a dose-linear increase in exposure without differences in QD and BID schedules

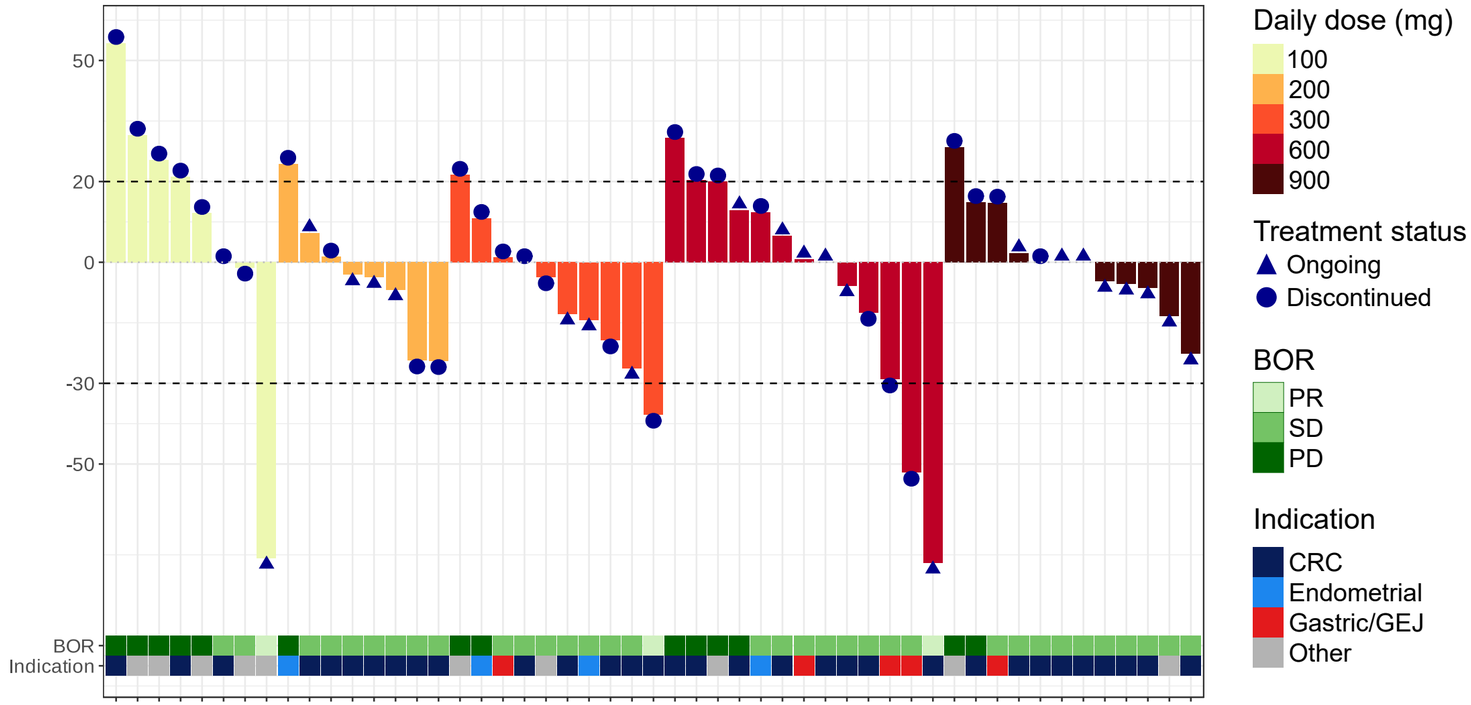


- QD dosing shows similar exposure as BID dosing, at equal total daily dose
- 2.1-fold accumulation was observed after repeated dosing on day 8 vs. day 1 in cycle 1
- Effective half-life = 19 hours
- Dose-linear increase in exposure up to 900 mg/day

Geometric mean plasma AUC (cycle 1, day 8) is shown.
AUC, area under the curve; BID, twice daily; QD, once daily; SD, standard deviation.

HRO761 shows antitumor activity with a high disease control rate

Best percent change in tumor lesions

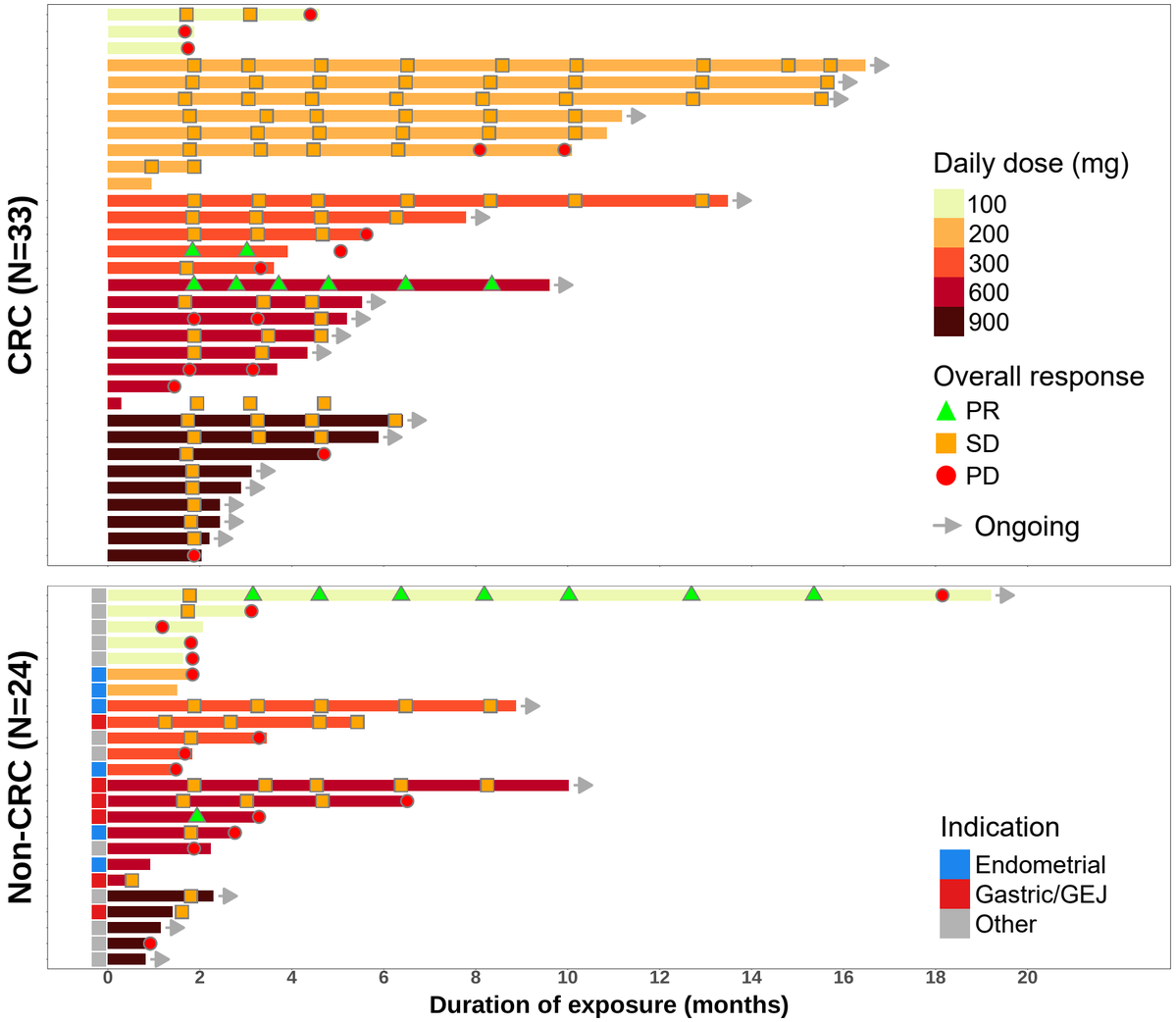


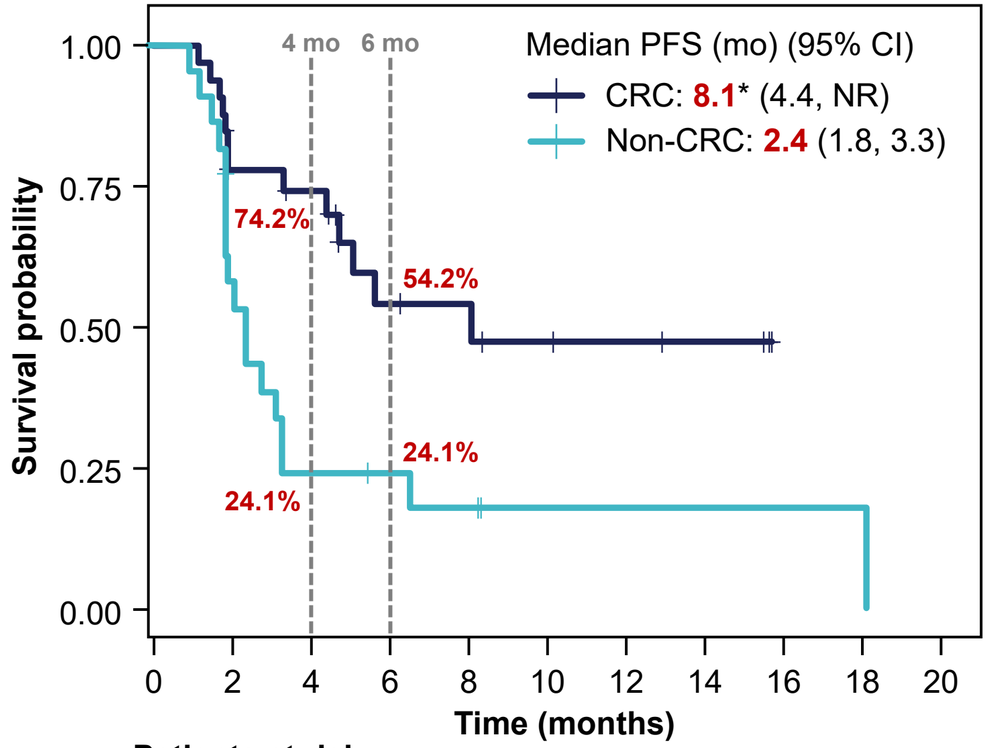
	CRC N=33	Non-CRC N=22	Total N=55*
BOR, n (%)			
PR	2 (6.1)	1 (4.5)	3 (5.5)
SD	24 (72.7)	10 (45.5)	34 (61.8)
PD	6 (18.2)	8 (36.4)	14 (25.5)
NE	1 (3.0)	3 (13.6)	4 (7.3)†
ORR, n (%) (95% CI)	2 (6.1) (0.7, 20.2)	1 (4.5) (0.1, 22.8)	3 (5.5) (1.1, 15.1)
DCR‡, n (%) (95% CI)	26 (78.8) (61.1, 91.0)	11 (50.0) (28.2, 71.8)	37 (67.3) (53.3, 79.3)

*2 ongoing patients were excluded as they had not yet reached the first post-baseline assessment at data cutoff.
†The 4 NE patients are not shown in the plot.
‡DCR = PR+SD. BOR of SD is defined as at least one SD observed 6 weeks or later from the first dose, without having a better response.

BOR, best overall response with confirmation; CI, confidence interval; CRC, colorectal cancer; DCR, disease control rate; GEJ, gastroesophageal junction; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Prolonged treatment duration and PFS in CRC patients





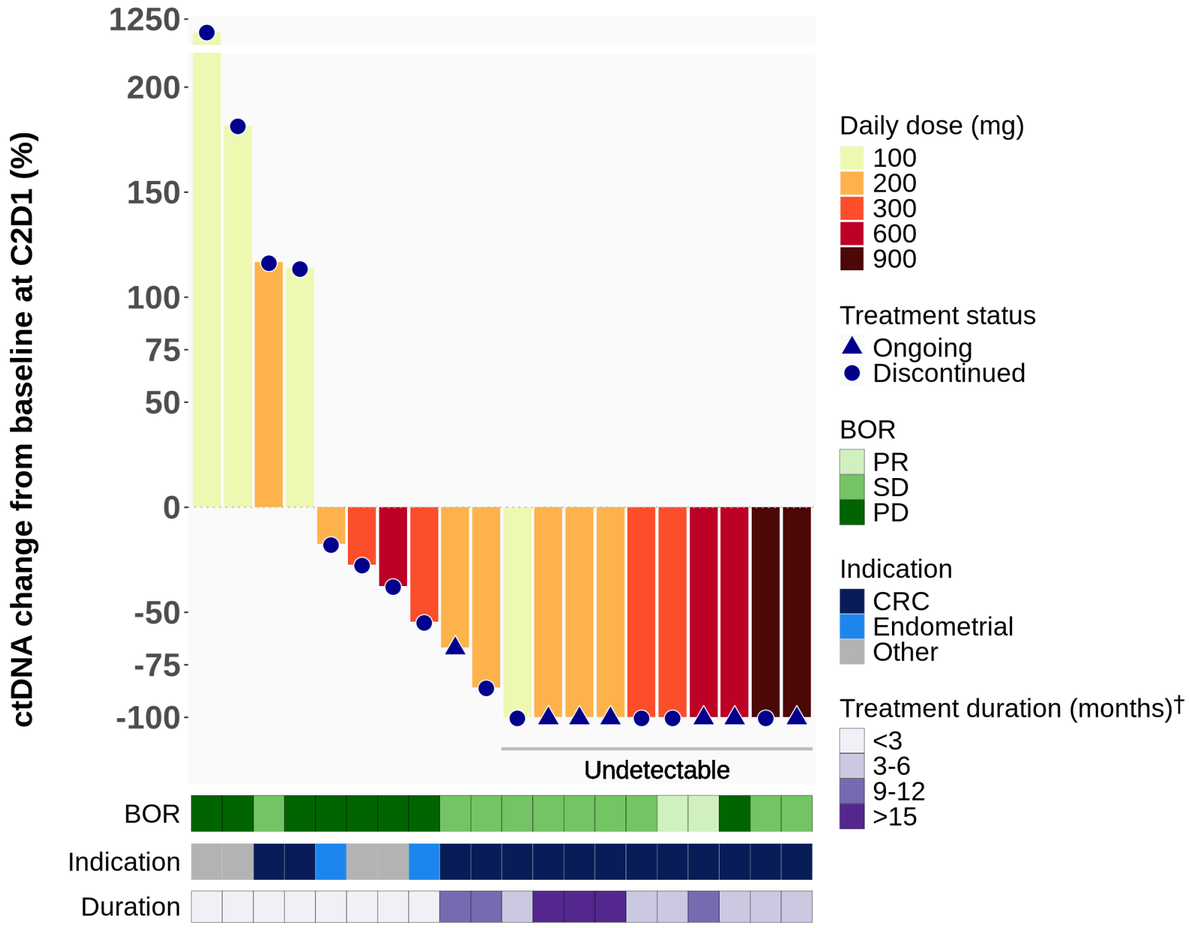
Patients at risk

CRC	33	20	18	10	8	6	4	3	0	0	0
Non-CRC	22	12	5	4	3	1	1	1	1	1	0

*Median PFS was not reached for the 30 CRC patients (18 ongoing) who received daily doses ≥ 200 mg.

CI, confidence interval; CRC, colorectal cancer; GEJ, gastroesophageal junction; mo, months; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

~70% of CRC patients with detectable ctDNA at baseline cleared after ~1 month on HRO761



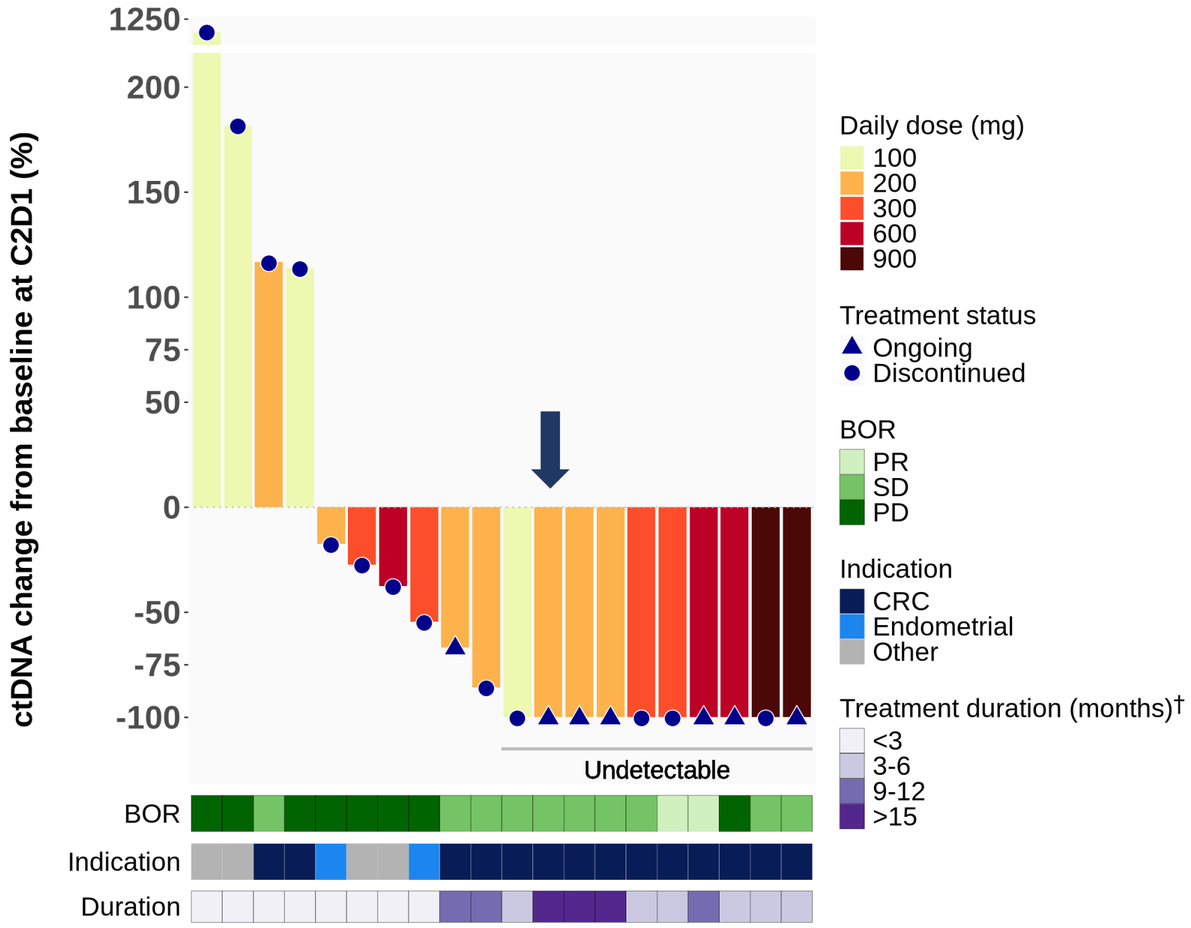
20 patients analyzed*

- 10 cleared ctDNA (all CRC, 2 PR, 7 SD, 1 PD)
  - 6 ongoing
    - 3 on treatment for > 15 months

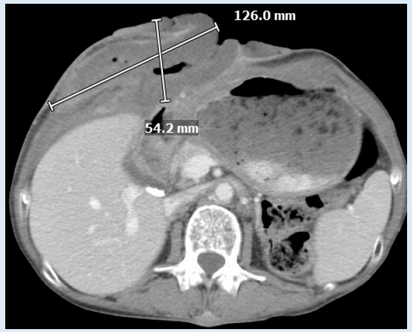
*Analysis performed for patients with detectable ctDNA at baseline for which a C2D1 measurement was available at data cutoff (n=20, no gastric/GEJ).
†There were no patients with treatment duration of 6-9 or 12-15 months at data cutoff; therefore, these categories were excluded from the plot.

BOR, best overall response with confirmation; C2D1, day 1 of cycle 2; CEA, carcinoembryonic antigen; CRC, colorectal cancer; ctDNA, circulating tumor DNA; GEJ, gastroesophageal junction; PD, progressive disease; PR, partial response; SD, stable disease.

~70% of CRC patients with detectable ctDNA at baseline cleared after ~1 month on HRO761



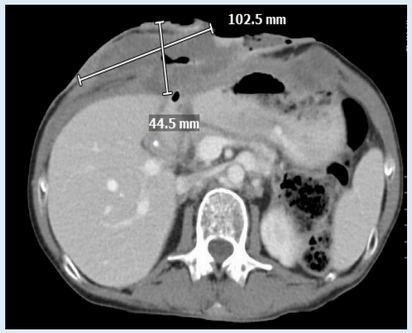
12.6 x 5.4 cm



A 53-year-old woman with stage IV MLH1/PMS2-deficient transverse CRC with PD on 5 lines of therapy

1.8 months HRO761

10.3 x 4.5 cm



- CEA 46 to 4.9
- ctDNA cleared
- BOR = SD
- > 15 months on therapy

*Analysis performed for patients with detectable ctDNA at baseline for which a C2D1 measurement was available at data cutoff (n=20, no gastric/GEJ).
†There were no patients with treatment duration of 6-9 or 12-15 months at data cutoff; therefore, these categories were excluded from the plot.

BOR, best overall response with confirmation; C2D1, day 1 of cycle 2; CEA, carcinoembryonic antigen; CRC, colorectal cancer; ctDNA, circulating tumor DNA; GEJ, gastroesophageal junction; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- In heavily treated post-CPI patients with advanced MSI-H/dMMR cancers, HRO761 shows:
  - A favorable safety profile
  - Dose-linear exposure with no differences between QD and BID schedules
  - Durable antitumor activity in CRC patients
- ctDNA analysis highlights deep molecular responses in CRC patients, including patients with SD by RECIST
- Data continue to mature, with over half of CRC patients on treatment at data cutoff

Future directions

- Randomized dose optimization of single agent HRO761 at 300 mg QD and 600 mg QD is ongoing
- Investigation of HRO761 in combination with pembrolizumab or irinotecan is ongoing

BID, twice daily; CPI, checkpoint inhibitor; CRC, colorectal cancer; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability-high; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

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